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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,182	01/18/2002	Pier Giuseppe Pelicci	0380-P02669US0	6367

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/937,182	PELICCI ET AL.	
	Examiner	Art Unit	
	J. E. Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,22,24,26-38,42-45,47 and 52* is/are pending in the application.

4a) Of the above claim(s) *1-8, 11, 13-18, 26, 28-35, 38, 42-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,12,19,22,24,27,36,37,47 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/26/2009 has been entered.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Status of the Claims

Claims 1-19, 22, 24, 26-38, 42-45, 47, 52 are currently pending.

Claims 1-8, 11, 13-18, 26, 28-35, 38, 42-45 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/9/2007.

Claims 9, 10, 12, 19, 22, 24, 27, 36, 37, 47, 52 are examined herein.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 10, 12, 19, 22, 24, 27, 36, 37, 47, 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of p66shc expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of p66shc expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of inhibiting the expression of p66shc in cells or tissues comprising contacting said cells or tissues with nucleic acid compositions that hybridize to sequences encoding p66shc (SEQ ID NO:2). The claims of the above invention are also drawn to methods of treating an animal having vascular complications of diabetes, wherein said compositions are administered to animals such that expression of p66shc is inhibited. The language of said claims encompasses both *in vivo* and *in vitro* activity. The specification discloses a working example where the p66shc gene is knocked-out in MEF cells (*in vitro*), as well as in transgenic mice (*in vivo)* wherein p66shc is not expressed due to disruption of the p66shc gene.

The specification does not provide any working examples demonstrating that antisense nucleic acid sequences can be effectively used in an animal to block p66shc expression sufficient

to result in the required outcome (e.g., treatment of disease, increase in resistance to oxidative stress, decrease in ROS). Furthermore, the specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its gene disruption models is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. It is acknowledged that one of skill in the art would recognize that antisense oligonucleotides could be used to inhibit expression of a target gene *in vitro*, in non-therapeutic methods, with a reasonable expectation of success.

The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) article by Braasch et al. emphasizes that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al.

goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective….several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378).

"[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death…oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable…antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro*

experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of p66shc expression *in vivo* using gene disruption techniques as being correlative or representative of the successful *in vivo* use of antisense compounds or treatment of any and/or all conditions or diseases suspected of being associated with p66shc expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

Furthermore, as indicated above, the *in vivo* results indicated in the working examples were obtained in knock-out mice. It is noted that Crystal (1995) teaches, "Humans are not simply large mice", and points out that, "predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials" (see pg 409, col. 1-2). Therefore, results obtained in mice cannot be extrapolated to humans with a reasonable expectation of success.

The claims are drawn very broadly to methods of treating cells *in vivo* or to treating or preventing a condition or disease suspected of being associated with p66shc expression in humans. Since the specification fails to provide any guidance for the successful treatment or

prevention of such a disease, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and/or tissues. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Response to Arguments

4. Applicant's arguments filed 6/26/2009 have been fully considered but they are not persuasive.

Applicants argue that a search of the USPTO.gov database for the term "antisense" in the claims reveals hundreds of issued patents directed to antisense molecules. This is not persuasive because every case is decided on its own merits. (*See In re Giolito*, 530 F.2d 397, 400, 188 USPQ 645, 648 (CCPA 1976):

> "We reject appellants' argument that the instant claims are allowable because similar claims have been allowed in a patent. It is immaterial whether similar claims have been allowed to others."

That other patents have been issued, based on different facts, is not evidence that the examiner's decision in this case, on these facts, is in error. Furthermore, the Examiner is not

asserting that all antisense technology is non-enabled. Rather, in view of the state of the art at the time of filing as evidenced by the references of record, the instant claims, are not enabled to their full scope for the reasons of record.

Applicants list 6 different companies that they describe as "actively involved in developing antisense therapeutics for the treatment of disease. Applicants also argue that a pubmed search of the term "antisense" revealed no less than 28,635 hits. Again, the Examiner's position is that the instant claimed invention is not fully enabled, not that antisense technology as a whole is non-enabled. Furthermore, it is pointed out that a search for the claimed invention in the databases including Pubmed as well as Patent databases revealed zero hits in the prior art. Therefore, although there may be over 28,000 database hits for the term "antisense", there are none in the prior art for the instantly claimed invention. Applicant is respectfully reminded that MPEP § 2164.01 indicates that the application, when filed, must contain sufficient information to enable one of skill in the art how to make and use the claimed invention to its full scope. In other words, the claims must be enabled at the time of filing.

Applicants argue that once an antisense molecule for a target is identified, routine methods are available for administering it to a subject and for assessing the subject for reduction in symptoms associated with disease. In response, it is respectfully pointed out that some claims are explicitly directed to therapeutic methods. Furthermore, the broad claims that do not specifically recite a therapeutic effect certainly encompass a therapeutic effect, and the specification discloses *in vivo* embodiments only as therapeutic methods. Therefore although methods of merely administering an antisense molecule to a subject and methods of assessing the effects of the administration on a disease *may* have been available, the references of record

demonstrate that there are a number of problems that must be overcome before an antisense molecule can be fully useful *in vivo* without an undue amount of additional experimentation, particularly with respect to treating and preventing disease.

Applicants argue that the additional experimentation that is required is routine, and the means for assessing the efficacy are disclosed. In response, considering the art-recognized problems with respect to using antisense oligonucleotides *in vivo*, and particularly with respect to treating disease, additional experimentation would be required. Furthermore, the additional experimentation would amount to trial-and-error experimentation without any guarantee of success, and any success would amount to a significant and unexpected advancement of the prior art. Therefore, the additional experimentation required for one of skill in the art to be able to make and use the claimed invention to its full scope is not routine, and amounts to an undue amount of additional experimentation. The fact that assays for assessing efficacy may be available does not provide an enabling disclosure for the claimed invention because merely assessing of the treatment was efficacious does not provide the guidance required enable the full scope of the instant claims. In other words, merely being able to determine if a treatment was effective does not provide the guidance necessary to overcome the problems recognized in the prior art.

Applicants argue that a 1992 article by Crooke describes in vivo application of antisense oligonucleotides which demonstrates that methods of in vivo administration were known in the art. Applicants point to page 342 of Crooke as evidence that the claimed method is enabled. However, page 342 of Crooke does not demonstrate that the antisense oligonucleotides were effective for inhibiting gene expression *in vivo*, nor does Crooke demonstrate how to overcome

the problems recognized in the prior art, such as indicated in the rejection. Furthermore, there is no indication that the antisense oligonucleotides were able to treat any particular disease, let alone any of the particularly claimed diseases. It is also pointed out that Crooke also recognizes problems with *in vivo* antisense therapy. For instance, on page 342, Crooke teaches,

> "Oligonucleotides of different types behave differently and there are substantial variations as a function of cell type. Moreover, length and specific sequences may alter uptake, and pendant modifications may profoundly influence cellular uptake."… "Mechanisms of uptake and distribution are poorly understood. Clearly, however, multiple mechanisms may play a role and different types of oligonucleotides may behave very differently."

Therefore, Applicants arguments, and the references submitted in support of Applicants position have been considered but are not persuasive.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 7:00 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner, Art Unit 1635